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Editor - Captain F. W. Farrar, MC, USN

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TABLE OF CONTENTS

Circular Letters:

NOTE

THE NEXT COURSE IN THE MEDICAL ASPECTS OF SPECIAL WEAPONS AND RADIO ACTIVE ISOTOPES FOR U. S. NAVAL RESERVE MEDICAL AND DENTAL OFFICERS AT U. S. NAVAL MEDICAL SCHOOL, NATIONAL NAVAL MEDICAL CENTER, BETHESDA, MARYLAND-

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Mumps Meningoencephalitis With and Without Parotitis: Only recently and in few accounts have clinical and epidemiologic observations concerning mumps meningoencephalitis been confirmed by adequate diagnostic evidence from the laboratory, in spite of general recognition that clinical manifestations are not always pathognomonic. Kane and Enders were the first to use serologic methods in a comprehensive study of the disease, and Henle and McDougall demonstrated the ease of virus isolation. In the present study of 25 patients with mumps meningoencephalitis, 13 with no enlargement of the salivary glands, conclusions were based on cases diagnosed by means of a combination of the newer technics of serologic study and virus isolation. These methods provide important tools for a closer understanding of the biologic aspects of mumps infections. The patients were followed in 2 Boston hospitals in 1948, a year particularly suited to the study because of the unusual prevalence of mumps in Massachusetts.

The clinical reaction that characterized these 25 patients with mumps meningoencephalitis was similar to that reported in recent summaries. Meningeal irritation was variously marked by headache, nausea, vomiting and nuchal rigidity. A few children had convulsions and delirium. One significant feature was the impossibility of distinguishing by clinical means between the signs and symptoms of patients with mumps meningoencephalitis and those of others who had serologically negative reactions for mumps and such clinical diagnosis as nonparalytic poliomyelitis and lymphocytic meningitis. Seven of 12 patients who had both meningoencephalitis and parotitis showed the 2 conditions on the same day. In 5 others parotid swelling preceded encephalitis from 5 to 9 days and had subsided by the time the patient came to the hospital. A few patients had sequelae. One, 2 years and 11 months of age, had weakness of the anterior part of the neck and abdominal muscles when seen later in a clinic for after-care of poliomyelitis. A 4-year-old boy had weakness of a leg a few weeks after his discharge from the hospital. Two patients were judged to have personality changes as a result of their illnesses, these being especially striking in a boy, 16 years old. The patients of this series ranged in age from one to 35 years, with 18 under 10 years and 5 who were 16 years or older. Most of the patients were male, only 5 of the 25 being female. The average duration of illness was 8 days.

A pronounced pleocytosis, with a high percentage of lymphocytes, characterized the spinal fluid of patients with mumps meningoencephalitis. Leukocytes exceeded 300 per cubic millimeter in 19 instances and were more than 1,000 per cubic millimeter in 9. No count fell below 100 per cubic millimeter in the first week of disease, and one reached a peak of 2,920 cells per cubic millimeter. Every patient showed 95 percent or more of lymphocytes at some time, although 4 of the 64 spinal fluids examined had percentages slightly below this figure. The leukocyte count tended to reach a high point sometime during the first week of the disease. Several lumbar punctures were ordinarily needed to bring out maximum values both for leukocytes and for total proteins. Maximum values for total proteins usually came later than those for leukocytes. Proteins were above 40 mg. per hundred cubic centimeters in 16 patients, 6 had values greater than 100 mg.,

and one patient had 253 mg. on the twelfth day. Leukocytes and total proteins of spinal fluids often persisted at abnormal levels after clinical recovery, in 4 patients for 2 weeks and more after onset and in one patient past the thirty-third day.

The antihemagglutination and the complement fixation tests gave comparable results. One or both tests showed a fourfold and usually a greater increase in antibodies when serums of the acute and convalescent phases were compared for all patients, except one, for whom serums from only the acute stage of illness were available.

Of 21 attempts to isolate mumps virus from patients with clinical mumps meningoencephalitis, all were successful. An initial belief that the first 2 or 3 days of the disease were most favorable for isolation of virus was not substantiated because 4 strains were obtained on the fifth and sixth days when the proportion of failures was no greater. The persistence of an abnormal spinal fluid suggests that mumps virus could be isolated from the spinal fluid occasionally in the second week of disease or even later, but this was not determined because, other than one specimen taken on the eleventh day, which proved negative, no specimens for virus isolation were collected after the sixth day. All spinal fluids were subjected to at least 3 passages in embryonated eggs. Mumps virus appeared on the first passage in 5 instances, on the second passage in 4, and on the third passage, twice. Six attempts to demonstrate mumps virus directly in the spinal fluid by agglutination of hen erythrocytes were unsuccessful. The mumps virus in cerebrospinal fluid can withstand storage under dry ice for long periods; the fluid of one patient yielded virus 5 months after first refrigeration. Mumps virus was isolated from the saliva of a patient on the second and fourth days of disease, in spite of an absence of enlargement of the salivary gland, although orchitis developed on the sixth day. Virus was not isolated from 4 other patients having no enlargement of the salivary glands when specimens were collected on the third, fourth, or fifth days of disease.

To test the hypothesis that invasion of the central nervous system is a primary feature of mumps infections, spinal fluids from 6 patients with early mumps parotitis and no evidence of meningeal involvement were examined for virus. The series of 3 egg passages made with each specimen gave a negative result.

A total of 12 patients (6 patients with uncomplicated mumps parotitis and 6 with disease of the central nervous system determined not to be mumps by serologic test) served as controls for the group with serologically proved mumps meningoencephalitis. Mumps virus was isolated from the spinal fluid of more than half of the patients with confirmed mumps infection of the central nervous system and in no instance from that of the control series.

The cases reported all occurred between March and November 1948, a year in which mumps was unusually prevalent in Massachusetts. Cases of meningoencephalitis associated with parotitis were scattered more or less regularly throughout the period, but 11 of the 13 patients with meningoencephalitis and no parotitis were seen from mid-May to early September. As the numbers are small, they may represent no more than chance distribution. The hypothesis is suggested, however, that enlargement of the salivary glands is a less frequent manifestation of mumps in summer than in winter. Johnson and Goodpasture, in the course of 3 years, found it difficult to induce parotitis in monkeys during the summer months. This may well be a factor in the rapid decrease of reported cases of mumps in warm weather, as mumps infection without glandular enlargement is difficult to recognize clinically. This absence of enlargement would have epidemiologic significance in explanation of the manner in which mumps virus is carried over in a population from one period of seasonal prevalence to another. Support for such an hypothesis requires further field and laboratory studies.

One might postulate an especially neurotropic strain of the mumps virus as responsible for an excess prevalence of simple meningoencephalitis that is presumably communicable. In all probability, the spread of mumps infection is not wholly by patients with parotid swelling. Mumps virus was isolated from 2 successive samples of saliva from a patient in the absence of enlargement of the salivary glands. A 16-year-old boy showed simple mumps meningoencephalitis in August, 3 weeks after his 15-year-old sister had an illness characterized by fever, apathy, headache and delirium of a week's duration and 2 weeks after a younger sister experienced a similar illness. In none of the children was salivary gland enlargement observed. However, 10 of the 13 patients with simple meningoencephalitis had a history of exposure to mumps parotitis from 3 to 4 weeks before onset. There is little factual evidence that mumps virus shows strain variations.

Mumps meningoencephalitis, with or without parotitis, is in certain years a common form of lymphocytic meningoencephalitis among children and young adults. Knowledge of the true incidence of this disease, especially when no glandular swelling is apparent, will await further application of newer diagnostic methods to a study of epidemics of mumps occurring within closed groups. No other encephalitis can be identified more readily by serologic methods, for the antihemagglutination test is simple and as satisfactory as complement fixation in establishing a diagnosis of mumps. A serologic test is indicated whenever appropriate signs and symptoms are associated with a spinal fluid having from 150 to 2,500 leukocytes per cubic millimeter, of which 95 percent are lymphocytes, and an elevated total protein content and, especially, with a history of exposure to mumps. These grouped findings are characteristic but not pathognomonic of mumps meningoencephalitis. Exceptions are few, either in the present series or in the fully substantiated cases of others. Full confirmation

of mumps meningoencephalitis is believed to rest on (1) the presence of abnormal cerebrospinal fluid findings and (2) a fourfold or greater increase of mumps antibody when serum from the acute phase is compared with specimens taken in convalescence. Successful isolation of mumps virus gives additional confirmation. Demonstrated abnormalities in the spinal fluid are important, because clinical findings, such as drowsiness, headache, nausea, and vomiting, occur in other conditions apart from a true encephalitis. A high titer of mumps antibody in a single convalescent phase serum may be misleading. Some patients of this series, who clinically did not have mumps, had a uniformly high level of antibody in both acute and convalescent phase serums. Acute phase serum should be obtained as early as possible, preferably within a few days of onset, because mumps antibodies are often present when active symptoms first appear.

Virus isolation from cerebrospinal fluid has been accomplished in only a few types of encephalitis of known origin. It has been demonstrated here, however, that virus can be isolated in 50 percent or more of spinal fluids taken in the first week of mumps meningoencephalitis. Whether mumps virus increases quantitatively in the spinal fluid during the first week of disease or is most prevalent at the onset is not known. Virus is demonstrable in almost all samples of saliva collected early in the course of mumps parotitis. It is likely, therefore, that something more than inadequacy of technic is needed to account for failure to demonstrate mumps virus in salivas from the patients tested who had meningoencephalitis without parotid swelling.

Mumps parotitis can be either apparent or inapparent. The patient in whom mumps virus was isolated from 2 successive samples of saliva collected when careful clinical observation revealed no enlargement of salivary glands presents evidence of the existence of inapparent parotitis. Henle and his coworkers also demonstrated this condition by isolation of virus from the saliva of children with artificially induced mumps. Thus, an inapparent parotitis can in some patients precede and in others accompany meningoencephalitis as apparent parotitis does. In a number of patients whose cases are presented in this report, a preceding parotid swelling had completely subsided by the time of admission to the hospital for encephalitis. Similar behavior by inapparent parotitis running its course prior to the onset of encephalitis explains the reason samples of saliva from 4 patients were collected too late to contain demonstrable virus. Isolation of virus from the saliva of one patient was favored by the simultaneous occurrence of inapparent parotitis and encephalitis. A further hypothesis is that involvement of the salivary glands, with or without swelling, is a primary feature of all types of mumps infection. Confirmation, or disproof, of these hypotheses awaits further investigation into the pathogenesis of mumps. (Am. J. Dis. Children, Sept. '49, L. Kilham)

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Treatment of Cutaneous Carcinoma with Podophyllin: The purpose of this preliminary note is to report brief observations from the Department of Medicine (Division of Dermatology) and the Department of Pharmacology of the Johns Hopkins University School of Medicine on the manner in which cutaneous carcinomas undergo involution following the topical action of podophyllin.

Podophyllin produces arrest of mitosis, distortion of nuclear pattern, and a chain of cytotoxic effects in the epithelium of normal skin as well as in the epithelial cells of any benign or malignant skin tumors with which it comes into contact for 8 hours or longer. There is abundant clinical and microscopic evidence that the drug's cytotoxic effects are more selective for certain types of epithelial cells, particularly those of moist, young, nonkeratinized acuminate condylomas, which are rapidly destroyed by a single application. By contrast the action on surrounding normal skin, unless excessive and unduly prolonged, is reversible as macroscopic and microscopic integrity of the skin is established soon after removal of the resin. Selective damaging effects on mouse tumors and on mouse tumor cells in tissue culture result from exposure to the drug. Podophyllin and podophyllotoxin are more toxic for recently weaned mice than for adult mice; the toxin is extremely toxic for chick embryos. Dry keratinized verrucae vulgares and chronic, or old, partially keratinized acuminate condylomas are resistant to the rapid necrotizing action. These facts indicate that the cellular destructive action is more selective for young, embryonic and tumor cells than for adult cells and that the changes produced in adult cells are reversible within certain limits.

The cancericidal potentialities were first pointed out when the similarity of colchicine and podophyllin effects was discovered. As a prelude to the clinical use of podophyllin for cutaneous carcinoma, sufficient data have accumulated in studies in the Johns Hopkins laboratory during the past 2 years to show that the topical application of podophyllin for prolonged periods is safe, provided contact with the eyes is avoided. The response of cutaneous carcinoma is slower than that exhibited by condyloma acuminatum and much more of the drug is required, but it appears from preliminary observations to be equally as impressive and as complete. Thus far 15 patients having a total of 25 cutaneous carcinomas have been treated. Biopsies were secured from each patient prior to treatment. Follow-up of 5 lesions was not accomplished because serial sections were excised at various stages of involution for microscopic analysis of treatment effects. Of the 20 lesions which were destroyed by multiple applications and permitted to heal, all except one showed satisfactory results. In this group there were 12 basal cell carcinomas measuring 0.5 cm., 0.8 cm., 1.5 cm., 1.5 cm., 1 x 2 cm., 2 cm., 2 cm., 2 x 2.5 cm., 2 x 3 cm., 2 x 3 cm., 2.5 x 3 cm., and 12 x 14 cm., respectively; 7 intra-epidermal carcinomas measuring 2 cm., 2 cm., 3 cm., 4 cm., 4 cm., 4 x 6 cm., and 8 x 14 cm., respectively; and 1 prickle cell carcinoma, 4 x 6 cm. The 12 x 14 cm. basal cell carcinoma was the only failure in the group. The resin was applied topically as a 25-percent suspension in mineral oil or a 20-percent solution in alcohol. Numerous treatment schedules

were tried; these varied from 2 applications in 7 days to 50 applications in 3 months. To date a satisfactory average schedule has not been determined but probably approximately from 10 to 20 applications within 3 weeks will be adopted as a working schedule based on current trial and error results. The periods of involution of treated tumors varied considerably. The most rapid disappearance was in 10 days; the slowest was 3 months. It must be emphasized, however, that varying experimental treatment schedules were being observed and that over-treatment in more than half of the cases undoubtedly prolonged healing in some cases. Including such variables the average healing time was 49 days after the first application. A most impressive clinical observation is the selective ulceration of tumor tissue; the borders of treated basal cell carcinomas are chanellized by the drug and the delineation of ulcerative moats outlining previous tumor sites is clear cut in contrast to the superficial and reversible signs of injury to the surrounding normal skin. The treated area heals with a pliant, slightly atrophic scar which resembles the cosmetically successful roentgen irradiation scar when it occurs without accompanying telangiectasia. The follow-up periods vary from one to 8 months with an average of approximately 6 months.

The results are encouraging, but it is obviously premature to express enthusiasm for the method until sufficient time has elapsed to determine whether the results will be permanent. Toxicologic, pharmacologic, and pathologic studies are being conducted in conjunction with clinical studies to ascertain the tolerance for the drug, the time factors, and amount of drug necessary to destroy cutaneous cancer permanently without causing irreversible damage to circumjacent normal tissue and at the same time to avoid hypersensitivity which is frequently produced by the drug. The selective topical effects of podophyllin differ from the effects of other chemicals such as those utilized in the chemosurgical method of Mohs, which produces nonselective tissue destruction that is measured by microscopic examinations of the fixed and damaged tissues as they are removed. The lack of available fixed tissue for microscopic examination during treatment may be an objection voiced by advocates of Mohs' chemosurgical microscopically controlled method. Therefore, it is not the intention of the author to recommend podophyllin as a treatment of carcinoma to supersede other well known methods such as surgery, roentgen therapy, electrodesiccation, cauterization, or chemosurgery. It is hoped that other investigators may explore this method, duplicating the author and co-worker's approach to the problem, which consists of excising treated tumors in various stages of involution and after healing to determine sequential microscopic signs of the tumor necrotizing effect and the permanency of the destruction.

Two other preliminary reports of the use of podophyllin in the treatment of cutaneous carcinoma and senile keratoses have been submitted recently by Dr. Leslie Smith of El Paso, Texas, and Dr. Fletcher Hall of Los Angeles, California, to the Archives of Dermatology and Syphilology. The results of Smith and Hall (In Press) are essentially similar to those herein reported. (Bull. Johns Hopkins Hosp., Sept. '49, M. Sullivan)

Studies on the Initiation of Blood Coagulation: Whole blood appears to contain all of the substances which are necessary for spontaneous coagulation. Blood obtained by technics designed to prevent contamination with tissue juice or other extraneous material will clot spontaneously in a glass receptacle. In the classical theories of blood coagulation the initiation of clotting is attributed to the presence of thromboplastin, a substance which has the property of converting prothrombin to thrombin. The fact that intravascular clotting does not normally occur leads to the belief that an appreciable amount of effective thromboplastin is not available in blood in vivo. The absence of effective thromboplastic activity from freshly drawn normal blood is further suggested by the great prolongation of the clotting time which is observed when blood is permitted to come in contact only with oiled or paraffined surfaces. Apparently, on contact with certain foreign surfaces blood may undergo a change in which effective thromboplastic activity appears. The present studies are concerned with the nature of the alteration which takes place in blood on contact with glass surfaces.

According to the classical theory of blood coagulation the source of thromboplastin in blood is believed to be the platelets. Although this belief has been widely accepted, some investigators have presented evidence suggesting that platelets are not necessary for the initiation of clotting. These workers believe that all of the components of blood required for spontaneous coagulation are present in platelet-free plasma. The use of silicone in blood clotting studies has greatly facilitated the investigation of this problem. Nevertheless, results obtained with this technic have been conflicting, and there is no agreement concerning the role of the platelets in the initiation of coagulation.

Previous studies have shown that when normal human plasma is rendered severely platelet-deficient, its clotting time in silicone-treated tubes is significantly longer than in glass tubes. Not infrequently essentially platelet-free plasma does not clot spontaneously in silicone-treated tubes although the same plasma clots readily in glass tubes. Contact of platelet-deficient plasma with a glass surface apparently results in an alteration which may not occur on contact with a silicone-treated surface. There are 2 possibilities concerning the manner in which glass surfaces serve to promote coagulation of essentially platelet-free plasma; either (1) a few platelets remain and are essential for the initiation of clotting, or (2) the clotting process occurs independently of platelets. In this study an attempt has been made to shed further light on this problem by observing the effects on coagulation of varying independently the concentration of platelets and the area of glass surface to which normal human plasma is exposed.

Essentially platelet-free plasma was prepared by high-speed centrifugation of human blood at low temperatures, using silicone-treated apparatus as previously described. No anticoagulant was employed. In most of these experiments the silicone-treated surfaces were reinforced by a film of silicone oil. During the preparation of the plasma its temperature was not permitted to rise above 2° C. Special precautions were taken during this centrifugation period to ensure that the temperature of plasma in the centrifuge cups did not exceed 2° C. Freezing of the plasma was

not permitted to occur. Platelet-rich plasma was obtained in the same manner by low-speed centrifugation. Plasmas with different platelet concentrations were prepared by mixing platelet-deficient and platelet-rich plasmas from the same source. Platelet counts on platelet-rich plasma were performed using Rees-Ecker diluent, and on platelet-deficient plasma by direct microscopic observation of the undiluted plasma as previously described.

Although some of the data presented in a number of previous studies which suggest that platelets are not essential for the initiation of coagulation are convincing, this conclusion has not been widely accepted. It is common belief that platelets are required for the initiation of clotting, but few investigators claim to have produced a spontaneously incoagulable platelet-free plasma from mammalian blood.

The data obtained in this study show that essentially platelet-free plasma was often spontaneously incoagulable in silicone-treated tubes, although relatively prompt clotting invariably occurred in glass tubes. The absence of clot formation in silicone-treated tubes indicates that neither effective thromboplastin nor thrombin was produced during the preparation of platelet-deficient plasma. However, the occurrence of clotting of centrifuged plasma in glass tubes does not provide absolute proof that the effect of glass surface is not mediated through the platelets because it is never possible to prove that platelets have been completely removed.

If the clot-promoting effect of glass surfaces is brought about by platelet disruption, it seems likely that a high concentration of macerated platelets would be very effective in accelerating coagulation. On the other hand increasing the area of the glass surface in contact with severely platelet-deficient plasma would be expected to have relatively little clot accelerating effect. This, however, was not the case. Increasing the glass surface area was much more effective in reducing the clotting time of platelet-deficient plasma than was the addition of high concentrations of platelets which had been macerated on glass surfaces. These observations suggest that the presence of a few remaining platelets is not concerned with the clot-promoting effect of glass surfaces on centrifuged plasma.

Crushed glass was more effective in shortening the clotting time of platelet-deficient plasma than was a suspension of macerated platelets. The clot promoting effect of crushed glass on centrifuged plasma seems better explained by an alteration produced in the platelet-free plasma itself rather than by disruption of a few remaining platelets. After storage for relatively short periods of time, plasmas often failed to clot on addition of crushed glass.

Although platelets appear not to be essential for the initiation of coagulation, they nevertheless play an important part in the clotting process. When

plasma clots on contact with glass, the rate of conversion of prothrombin to thrombin is directly related to the platelet concentration. The clot-accelerating effect of platelets is not appreciable in plasma which is protected from contact with glass and similar surfaces. For rapid conversion of prothrombin both the surface factor and platelets are required. Plasma which has been stored for relatively short periods of time may not clot on contact with glass. This observation suggests that the clot-promoting effect of glass is mediated by a labile component of plasma. Tests to determine the reactivity of plasma to glass surfaces evidently should be carried out while the plasma is fresh.

Platelet-free plasma is definitely hypo-coagulable as compared with normal plasma. In experiments to determine whether such plasma contains all of the substances necessary for spontaneous coagulation, optimal conditions for clotting must be provided. Those investigators who have reported that platelet-free plasma is spontaneously incoagulable have apparently not tested their plasmas under such optimal conditions. In the reported experiments, suboptimal temperatures and minimal glass surface area have been employed. The experiments described in the present report show that if coagulation of platelet-deficient plasma is sufficiently delayed, the plasma does in fact become spontaneously incoagulable, presumably because of deterioration of a plasma component.

Students of blood coagulation have for years been troubled by the problem of complete removal of platelets from plasma. It is implied in a recent report that many hours of centrifugation at high gravitational forces are required to remove all of the platelets from normal plasma. However, in the present experiments approximately 99.995 percent of the original number of platelets in normal blood were regularly removed by centrifugation for only 10 minutes at about 17,500 g. Furthermore, on direct microscopic observation of the undiluted centrifuged plasma the few platelets remaining were observed to settle to the surface of the counting chamber. No evidence was found to support the belief that these platelets were remarkably less dense than the average platelets. It seems likely that these platelets were derived from the centrifuged sediment as a result of the slight agitation inevitably produced by withdrawal of the supernatant plasma.

The manner in which glass surfaces promote coagulation of platelet-free plasma remains to be clarified. It appears that on contact with glass, plasma undergoes a change in which effective thromboplastin is made available. Studies on patients with certain disorders of blood coagulation make it seem likely that a specific protein is present in normal blood as an inactive thromboplastin and is converted to an active form on contact with a glass surface. No evidence was found that glass surfaces affect the final stage of coagulation. (Bull. Johns Hopkins Hosp., Sept. '49, R. C. Hartmann et al.)

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Studies on the Effect of Aureomycin in Syphilitic Infections: Many reports have appeared on the efficacy of aureomycin in various bacterial, viral, and spirochetal infections. O'Leary, Kierland, and Herrell reported 2 patients with early syphilis, and Irgang and Alexander 9 others, treated with aureomycin with favorable results. Organisms disappeared from open lesions in approximately from 2 to 5 days, lesions healed, and positive serologic tests reverted to or toward negative. Unpublished experiments of Nelson indicate that, in vitro, aureomycin has only one thousandth the treponemal immobilizing effect of penicillin (0.1 gamma of penicillin G per milliliter was equivalent to 100.0 gamma of aureomycin). Nelson's work was followed by observations on the activity of the drug in rabbit and human syphilis, which are reported in the present communication.

Aureomycin is effective in experimental rabbit syphilis, both in the treatment of established early infections and in abortive (prophylactic) treatment. In both early abortive and later treatment, the minimal effective dose has not yet been determined. Treponemes disappeared as rapidly from open lesions after a total dose of 50 mg. per kilogram as after 4 times this amount, and animals were as readily protected after 250 mg. per kilogram as by 850 mg. per kilogram. Aureomycin, given intramuscularly to rabbits in total doses of 50, 100, and 200 mg. per kilogram, produced a decrease of from 50 to 90 percent in the number of treponemes in cutaneous syphilomas in 48 hours. Complete healing of the lesions occurred in about 10 days. Aureomycin in doses of 12.5, 25, and 50 mg. per kilogram given twice daily for 8- and 10-day periods prevented the development of syphilitic orchitis following the intratesticular inoculation of an emulsion of T. pallidum.

Because lymph node transfers were not made in the animals with established infections, and are not yet available in the group given early abortive treatment, it has not been determined whether cure of established infections was accomplished, nor whether delayed or asymptomatic infections may not yet appear in the group given early abortive treatment.

Orally administered aureomycin in daily dosages of 2 or 4 Gm. resulted in the disappearance of T. pallidum from the lesions of early syphilis in 4 of 9 patients observed for 48 hours, in 6 of 6 observed for 72 hours, and appeared to produce local healing at the end of 144 hours in 2 of 6 patients.

In animals or man the effect of aureomycin, in the dosages and by the routes employed, is slow relative to that of penicillin as measured by the disappearance time of organisms from open lesions and by the rate of healing. Though definite comparisons of the minimal effective dose cannot be made at the present time, because that for aureomycin is not yet known, the in vitro data suggest that, in gravimetric terms, aureomycin may be less efficient than penicillin. Dosage comparisons between animals and man may be difficult to assess. The authors have administered the drug to rabbits by the intramuscular

route because in the rabbit oral administration is difficult, and gastric physiology and perhaps absorption are different in the rabbit and in man. The oral route has been used in man because of the intense local pain produced by intramuscular injections, and the satisfactory results of oral administration in other infections.

Lacking more definite information concerning minimum effective dose of aureomycin in syphilitic infection in animals and man, concerning the comparative effectiveness of aureomycin and penicillin, and concerning final proof of cure or protection in animals, the authors have felt it undesirable to depend on aureomycin alone in the treatment of infected human beings, to all of whom a subsequent course of penicillin has been given. Moreover, considering the frailty of human nature, the authors still believe it to be undesirable to rely on any oral medication for the cure of syphilis in man, unless and until it can be shown that a single pill or capsule, swallowed under observation, is curative. For the present, therefore, the use of aureomycin in the treatment of syphilis should, in the authors' opinion, be confined to further experimental studies. If aureomycin is used for the treatment of any other venereal disease, because it appears to be effective in all, the possibility of suppression of simultaneously acquired but not yet evident syphilis must, as in the penicillin treatment of gonorrhea, be kept in mind. (Am. J. Syphilis, Sept. '49, R. H. Wiggall et al.)

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Prophylaxis of Venereal Disease with Oral Penicillin in the U. S. Navy: Oral tablets of penicillin 100,000 units, 200,000 units, and 250,000 units have been shown to be highly effective in the prevention of gonorrhea if taken within a few hours after exposure. Reductions of 90 percent or more in the incidence of infection have been observed in 2 studies when the tablets were taken at the time of return to the ship, and reduction of 58 percent was observed in a study in which the tablets were taken the morning after the day on which exposure occurred. Results to date have been based on actual occurrences of relatively small numbers of cases in the treated and the control groups.

The establishment of control groups which exactly duplicate the groups receiving tablets is impossible without the use of placebos. The use of placebos for extended studies is not feasible because of the observed tendency of many men to rely on the tablets alone for prophylaxis; it was observed in one study that 22 percent of the men who formerly used standard Navy prophylaxis discarded it within 2 months from the time oral penicillin tablets were made available. Because of this, no further studies using placebos will be conducted.

Future studies will have to be based on the incidence rates incurred before and after instituting oral prophylaxis in a vessel or squadron operating in the same general area, or on differences in rates between comparable vessels in the same area, some of which use oral penicillin prophylaxis in evaluation studies and some of which do not. A third method of determining the efficacy

of the measure, although less accurate than the other 2, is the direct observation of the results in each man who takes oral prophylaxis. This method requires an accurate record of each liberty taken by every man who participates in this study whether or not a tablet was taken and whether or not exposure is admitted.

In view of the high cost of oral tablets of penicillin (about 22 cents each, but with a prospect of somewhat lower prices in the future) a careful accounting for every tablet dispensed is considered necessary. These tablets are further highly prized in black market trading and if they are made freely available, they may be widely utilized in self-treatment in cases of manifest venereal disease. In addition to the accurate accounting in the case of every tablet used, each tablet should be swallowed in the presence of a Medical Department representative. Oral penicillin tablets should be handled with the same strict accountability as is required for medicinal alcohol.

The Bureau of Medicine and Surgery has prepared convenient record cards for tabulating liberty, exposure, and prophylactic history in individual men utilizing various prophylactic methods. These cards or similar ones should be used in every instance in which oral prophylaxis with penicillin is instituted, until enough information has been accumulated to answer the following questions:

(a) What are the time to dose relationships in the prevention of gonorrhea?

(b) Do the tablets protect against syphilis?

(c) Do the tablets protect against the other venereal diseases?

(An affirmative answer is not anticipated in the case of penicillin, but it possibly may be expected in the case of aureomycin.)

(d) To what extent does the institution of oral penicillin prophylaxis lead to voluntary abandonment of standard Navy prophylaxis, and to what extent does this lead to a rise in the incidence of chancroid, lymphogranuloma venereum, granuloma inguinale, and nonspecific urethritis of one or more unknown causes?

(e) To what extent do these tablets mask syphilis and to what extent in practice may they alter urethritis caused by Neisseria gonorrhea so that diagnosis is made difficult?

(f) What is the likelihood that penicillin-resistant strains of N. gonorrheae will be produced?

Much additional information will have to be assembled before oral prophylaxis can be approved apart from some effort at scientific study.

In view of the low venereal disease incidence in the continental United States, it is estimated that perhaps more than 200 tablets would have to be given in order to prevent one case of venereal disease. Because of the present high

cost, this prophylactic measure given at Navy expense cannot be justified now in areas of low incidence. In view of the grave hazards of self-treatment, including complications and further spread of venereal disease resulting from inadequate treatment, the sale of these tablets over the counter without prescription and in vending machines is forbidden. (Preventive Medicine Div., BuMed)

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Recommended Treatment in Syphilis and Gonorrhea: See copy of BuMed Circular Letter No. 49-116 on page 25. Copy of this letter likewise appears in the Navy Department Bulletin of 30 September 1949.

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Incidence of Venereal Diseases inthe U. S. Navy: Of outstanding significance in the incidence of venereal diseases in the naval service was the war record. Figures compiled from the Fa-card (Individual Statistical Report of Patient) show that the annual incidence rate for venereal diseases fell from 88.5 per 1,000 in 1940 to 54.9 in 1941, and then continued a steady decline over the war years, reaching a low of 30.8 per 1,000 strength in 1944, with a rise to 35.2 in 1945. At no time in the history of the Navy had the over-all rate for venereal disease been as low.

During the year immediately following the cessation of hostilities venereal disease incidence rates increased sharply, this increase being apparent in all areas, with rates for the noncontinental areas and ships running considerably higher than for continental stations. The total incidence rate for all ships and stations reached a high of 109.6 in October 1946; the rate for ships reached a high of 173.2 per 1000 in November 1946, and the incidence rate for the continental and noncontinental areas reached their peaks of 73.5 and 139.9, respectively, in October 1946.

Since 1946 the general trend in venereal disease incidence rates has been downward, with any rise closely followed by a further decline; the overall rate for June 1949 was 42.8 per 1000 strength, which is the lowest since the war.

From the high point reached in late 1946 through June 1949, the continental districts showed a decline to the present rate of 25.5 per 1000 strength, the lowest reported from any area. The noncontinental areas with a rate of 46.2 and ships with a rate of 72.0 per 1000 average strength for the same month evidence comparable improvements. These rates indicate a reduction of approximately 60 percent from the rates reached in 1946. The highest venereal disease rate is still being reported from ships, the present rate of 72.0 per 1000 strength being more than two and one-half times that for continental districts, and somewhat over one and one-half times that for noncontinental areas. (Statistics of Navy Medicine for October 1949)

The Corticoadrenal Factor in Hypertension: There are several reasons why an investigation of the corticoadrenal function in essential hypertension seems of interest. They can be briefly summarized as follows:

1. Experimental renal hypertension produced by the Goldblatt clamp is greatly diminished or disappears after bilateral adrenalectomy in dogs whose life is maintained by cortical extracts. Whether this results from a specific action of the cortex on renal hypertension or the general changes produced by adrenalectomy is uncertain, but it seems that in adrenal insufficiency there is a reduction of sensitivity to the pressor effect of renin. This has been explained by the fall in concentration of hypertensinogen in the blood, which returns to normal on administration of cortical extracts or desoxycorticosterone.

2. According to the concept of Selye, hypertension is an expression of the general adaptation syndrome. In his animal experiments corticoadrenal stress as manifested by storage and elimination of cortical lipids and decrease in the lymphocytes in the blood is an essential part of the alarm reaction.

3. Epinephrine infusion or splanchnic nerve stimulation may cause increased corticoadrenal secretion; splanchnic nerve section, however, does not interfere with the basic corticoadrenal output. This effect is demonstrated by the decrease of the cholesterol and ascorbic acid content of the gland, but mediated through anterior pituitary action.

4. In man, some authors believe that the incidence of hyperplasia or adenomatous change in the adrenal glands of hypertensive patients is higher than in the control group; this is denied by others.

5. The full-blown Cushing's syndrome shows a plasma electrolyte disturbance which is diametrically opposed to that seen in Addison's disease. Experimentally, the overactivity of the eosinophil cells of the anterior pituitary gland, which are trophic to adrenal cortex, produces diastolic hypertension no matter how this eosinophil preponderance is produced.

6. In a hypertensive patient a subsequently developing Addison's disease produced a normal blood pressure, as long as the patient was kept on salt alone; when desoxycorticosterone was administered the elevation of blood pressure returned. When normal individuals are subjected to a sudden withdrawal of sodium, they lose water, weight, and go into a syndrome characterized by increased sweating, insomnia, and extreme weakness; but in essential hypertension this does not happen. The patients lose minimal weight and are asymptomatic. This may be due to renal changes or the changes in the kidney mediated by adrenal cortex. The low sodium diet or the low protein rice diet may well act through the adrenal cortex. Desoxycorticosterone acetate when administered intravenously acts as a pressor substance in hypertensive individuals.

In previous reports, the author pointed out that a small group of juvenile or middle-aged hypertensive patients exist who in spite of favorable preoperative studies fail to show a favorable response after operation; others show a delayed response, appearing as late as 6 months after operation. For this reason it was decided to study a group of hypertensive patients in regard to their corticoadrenal function.

Hormonal studies were not within the scope of the laboratory. As a matter of fact, the sex hormone production is said to be diminished in hypertension and during the general adaptation syndrome the sex hormone production is not stimulated at the expense of sugar active and salt active corticoids. The 11 oxysteroids, which increase sevenfold on the administration of adrenocorticotropic hormone, were not studied. The methods of the author and co-workers were so selected that first a simple test was made for purposes of orientation and when this was found to be positive, other methods were used to corroborate the suspicion that adrenocortical hyperfunction might be present.

In 1934 Fenn, Trump and the author described a test for insulin sensitivity and summarized the previous literature. The aim was to distinguish an insulin-resistant from an insulin-sensitive diabetic patient. A group of factors was listed which were known to increase the action of insulin, such as thyroidectomy, hypophysectomy, pancreatectomy, high carbohydrate diet, and alkaline diet. To these, animal experiments added celiac ganglionectomy, adrenal denervation, and splanchnic nerve section. One factor which has since then become known mostly through the work of Jensen and Grattan is the glycotropic, anti-insulin substance of the anterior pituitary gland which requires the presence and functional activity of the adrenal cortex. Heinbecker and Rolf showed that the anti-insulin factor resides in the eosinophil cells of the anterior pituitary gland. It is likely that many of the factors listed in the previous publication of the author and co-workers act through this mechanism.

The original test called for an injection of 0.01 unit of insulin per kilogram of body weight, given intravenously, but because most workers adopted a tenfold dose and because insulin resistance is thus more strikingly demonstrable, a dose of 0.1 unit of insulin per kilogram of body weight was used in the present studies.

The test at present consists of the determination of a fasting blood sugar, after which insulin is injected intravenously. Blood sugars are determined one half, one, 2, and 3 hours after the injection. In a group of typical responses to this dose of insulin in hypertensive individuals, some curves showed a good response at 30 minutes, with rapid recovery of the blood sugar level in from one to 2 hours; one curve showed a delayed response which did not appear until one hour after injection, and one curve showed a complete resistance to this dose of insulin. Curves may also show a normal dip but a failure of normal return to

the fasting level of blood sugar. As a recent refinement of the insulin tolerance test, the rate of fall in reducing substances was studied by taking samples at short intervals, especially at 10 and 20 minutes. A delay in the fall was observed in malignant hypertension and acromegaly.

Insulin tolerance curves were determined on 50 consecutive hypertensive patients during their preoperative study. Of these, 31 showed a normal response, 4 showed a delayed response, 7 showed an early dip and returned faster than usual to normal, and 8 showed no response at all. Obviously, another possible curve exists, namely, a poor response to the insulin hypoglycemia by failing to rise from the initial dip. Such curves are seen in Simmonds' pituitary cachexia and in Addison's disease. Interestingly enough, patients who show a great deal of fatigue and listlessness after operation may present such a slow rise following the hypoglycemic dip; their convalescence may be greatly hastened by cortical extract.

The 8 patients exhibiting insulin resistance were of particular interest. If their insulin resistance was really due to an increased pituitary corticoadrenal activity, what other tests could be used to confirm this assumption and what was their postoperative course? The following additional tests were done in the insulin-resistant group of hypertensive patients:

The Intravenous Sugar Tolerance (Soskin). Fuller Albright and his coworkers stated that the sugar hormone of the adrenal cortex is responsible for the corticoadrenal symptoms in the Cushing's syndrome. For this reason, in patients who were suspected of corticoadrenal stress, a sugar tolerance curve was obtained. But because the tests were to be repeated after operation and because splanchnic nerve section accelerates upper gastro-intestinal motility, it was felt that the intravenous route would eliminate the different rates of absorption from the gastro-intestinal tract. The patients were given one third Gm. of dextrose per kilogram of body weight intravenously in 50-percent solution. Blood sugars were determined before and 30, 60, and 120 minutes after the injection. One patient showed a complete insulin resistance prior to operation. Three months later the insulin resistance diminished and the patient was sugar-free on a liberal diet without insulin. Desoxycorticosterone acetate which has a definite pressor effect in hypertensive patients showed no effect on the intravenous sugar tolerance. It is obvious that this synthesized product is by no means equivalent to the full activity of the adrenal cortex; besides, the salt hormone should not affect sugar tolerance.

The Water Tolerance. Fasting subjects are given 1,500 cc. of water to drink in from 20 to 30 minutes, after being deprived of water and food for 14 hours. The bladder is emptied just before ingestion of the water and thereafter every 30 minutes for 4 hours. Volume and specific gravity are determined for each individual specimen. Normal subjects eliminate from 1,200 to 1,500 cc. of urine; the specific gravity fluctuates inversely with the output. It was originally

thought that this test would give a measure of salt and water retention and thus relate to the salt-water hormone of the adrenal cortex. Truly enough this was illustrated in one patient who was not only partially insulin-resistant but who had a large corticoadrenal adenoma removed during the second stage of splanchnic nerve section. It became obvious, however, that in the average hypertensive patient without corticoadrenal involvement, this is an excellent renal function test and that patients can be readily grouped into 6 patterns. The value of these patterns, which are described in another article (page 19), lies in establishing a type of renal impairment which seems uninfluenced by splanchnic nerve section and thus is significant in predicting a poor result.

Trials were made with the salt tolerance test of Soffer, with the uric acid-creatinine ratio of Thorn, and the NaCl ratio of Selye. Either they were not simple enough for the purpose of this experiment or there is as yet insufficient experience to evaluate their significance.

Limited experience with the simple clinical tests (insulin, sugar, and water tolerance) indicates that 8 of the group of 50 patients have shown corticoadrenal hyperactivity; interestingly enough, if this is due to simple hyperfunction, splanchnic nerve section diminishes this activity gradually over a period of from 3 to 6 months. That the adrenal cortex is influenced by sympathetic activity has been suggested by some of the early histologic studies of the author and coworkers with Cuthbert and recently persuasively proposed by Vogt and by Long. There still remains the hormonal action of the eosinophil cells of the anterior pituitary gland on the adrenal cortex and also the autonomous activity of a corticoadrenal adenoma.

From a practical standpoint in patients with hypertension, a negative response from the simple insulin tolerance test is suggestive of corticoadrenal hyperfunction. In such hypertensive patients one may find corticoadrenal adenoma or a simple hypertrophy. Whether a bilateral partial resection of the adrenal gland should be done, as advocated years ago by De Courcy, or whether splanchnic nerve section *per se* will bring about a slow involution is yet to be determined. At any rate, there are now simple methods for investigating this factor.

There has been no correlation as yet between the insulin-resistant patients and those patients who respond to sodium restriction, but it is possible that this would be a simple way to select hypertensive patients for such a diet if it could be shown that sodium restriction acts through dampening the corticoadrenal factor as suggested by Grollmann and associates. Also, the group of hypertensive patients who have not responded well to splanchnic nerve section and yet do not show extensive adrenal damage may well be benefited by such a procedure.

Attention should be called to the results from water tolerance studies which seem to have prognostic value before operation in patients with hypertension.

The corticoadrenal factor, the posterior pituitary factor (which has not been discussed here), and the renal factor are all at play; however, certain curves are so suggestive of late nephrosclerosis that together with the results of other renal function tests they form a contraindication to operation.

In summary, there are experimental data and clinical observations recorded in the literature which suggest that corticoadrenal activity is a factor at least in some cases of hypertension; insulin resistance means an activity of pituitary eosinophils, mediated through the adrenal cortex; the sugar tolerance in corticoadrenal stress seems to be diminished, just as in acromegaly; and the water tolerance, dependent on a number of factors, is a sensitive index of renal function and has prognostic value concerning the expected results from splanchnic nerve section. (Surgery, July '49, G. de Takats)

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Relation of Patterns of Water Tolerance to Operability in the Hypertensive Patient: In previous communications the authors have stressed the importance of rigid selection of hypertensive patients for sympathectomy. The grading of the patients into 3 well-defined groups as shown below has been of definite value. Irreversible cerebral, cardiac, renal, or peripheral vascular damage makes surgery ineffective. It seems, however, that the functional state of the kidney, whether involved as a primary or a secondary factor in hypertension, needs closer attention. Clinical tests, readily performed in hospital laboratories, consist of the concentration-dilution test, the 15-minute phenolsulfonphthalein test, and the urea clearance test. Except in a few research institutions, the inulin and inulin-Diodrast clearance has not proved to be of practical applicability, although the recently simplified technic of Landowne and Alving seems to be of definite promise. The authors concluded that the customary concentration-dilution test could be made more sensitive by collecting half-hourly samples during the period of dilution, and testing them for volume and specific gravity. This is the water tolerance of Adelsberg and Fox, who applied it for the study of patients recovering from hepatitis.

Group 1. Age below 40. Minimal or no detectable organic damage. Normal blood pressure on complete rest or barbiturates. Casual diastolic pressures above 100 millimeters of mercury.

Group 2. Age from 20 to 55. Moderate vascular sclerosis in all organs. Well-demonstrable angiospasm. Diastolic pressures cannot be lowered below 110 mg. Hg by any method. Rising diastolic pressure during the course of last six months.

Group 3. Large recurrent retinal hemorrhages and exudates or papilledema. High fixed diastolic pressure which cannot be lowered below 120 mm. of mercury. Congestive or anginal heart failure. Poor renal function. Numerous cerebrovascular accidents. An actual malignant or premalignant state of hypertension with continuous maximal angiospasm uninfluenced by either pressor or depressor stimuli.

The authors present different patterns of curves representing water tolerance, correlated with the hypertensive status and the postoperative course of 100 patients and then attempt to analyze the factors influencing such tolerance curves.

In this test, the patient receives nothing by mouth after 6 p.m. the night before. No urine is saved until 8:00 a.m., at which time the bladder is emptied and a specimen kept for examination. Then 1,500 cc. of water are consumed within one half hour. No breakfast and no other liquid are permitted. Urinary samples are collected at half-hour intervals between 8:00 a.m. and 12:00 p.m. They are tested for volume and specific gravity. Normal subjects eliminate from 1,200 to 1,500 cc. of urine, with the peak in the first 2 hours; the specific gravity fluctuates inversely with the output.

The authors were anxious to know whether a weighed sodium and water intake prior to the test was necessary, and hence determined a few curves after sodium restriction and after excessive sodium and water intake. It did not seem that the normal individual was affected by these measures; it is sufficiently known, however, that the hypertensive individual tolerates salt restriction far better than the normal person. A water tolerance test indicating unusual sodium and water retention was only considered significant for corticoadrenal activity when the patient showed a decreased response to insulin, an abnormal sugar tolerance curve, or both. Such was the finding in the case of a patient who had a left-sided corticoadrenal adenoma, proved by operation. Desoxycorticosterone acetate has a similar effect on the curve of water excretion.

An inhibition of diuresis is also accomplished by the antidiuretic hormone of the pituitary, whose secretion is inhibited whenever water is ingested. Such a curve is shown after the injection of 1.0 cc. of Pitressin one-half hour before the water tolerance is started. If a type of human hypertension exists which is mediated by the antidiuretic hormone, this should be demonstrable in the blood as Griffith and his associates have postulated for a certain group of patients. The authors state that they have no experience with this method.

Water tolerance in hepatic disease has been studied by Adelsberg and Fox, who found significant changes in diuresis during different stages of liver disease. In the present group of patients hepatic damage could be excluded, with the exception of the middle-aged, alcoholic, atheromatous hypertensive persons, in whom operation is not advocated.

The renal factor proved to be the most significant in this group of hypertensives who were studied for their operability. It has been the experience that of all the irreversible factors which are encountered in essential hypertension, the renal damage is most important because, aside from the early vascular changes which may be present on a functional basis and produce corticorenal ischemia, the fixed vascular and parenchymal damage in the

kidney seems to be least capable of improvement compared with the regression in the eye grounds, diminution in the size of the heart, or the changes in the electrocardiogram toward normal which follows splanchnicectomy.

Patterns of Water Tolerance. From the standpoint of renal function, the simple concentration-dilution test has not been as sensitive an index as the water tolerance. After employing this test routinely for the past year in preoperative studies in over 100 patients, 6 patterns have appeared in the curves representing specific gravity and volume.

Pattern 1. This corresponds to the normal water tolerance; for example, the specific gravity curve starts with 1.015 and is regained in 4 hours. Water excretion occurs early, and after 2 hours not much urine is obtained. The urine shows no pathologic elements. The phenolsulfonphthalein excretion is always above 30 percent and sometimes as high as 40 percent in 15 minutes. The urea clearance is above 40 cc. per 100 cc. of blood.

Pattern 2. The specific gravity curve, starting between 1.015 and 1.020, drops to low figures and is only slightly regained. The ingested water is overexcreted. There is a considerable excretion of urine in the first 2 hours, and a plateau is not infrequent. The 15-minute phenolsulfonphthalein excretion in this group is just as high as in the first group, varying between 30 and 45 percent. The urea clearance is above 40 cc. per 100 cc. of blood standard clearance.

Pattern 3. The specific gravity starts high, then drops and is hardly regained. Water excretion is definitely delayed, a shift to the right being obvious. Ingested water is overexcreted. Phenolsulfonphthalein excretion in fifteen minutes is still above 30 percent and the urea clearance is widely fluctuating. Renal biopsies show more damage than in the previous groups.

Pattern 4. There is a beginning fair concentration which drops to a dilution level which is maintained throughout. Water elimination occurs late, between the third and fourth hours. There is no overexcretion of water. The 15-minute phenolsulfonphthalein excretion is never above 20 percent; the urea clearance varies. Renal biopsies show Grade 3 nephrosclerosis.

Pattern 5. In this pattern there is a high concentration which promptly drops to a high dilution level, but never rises again. Water excretion starts after one hour, but is remarkably stable, the volume remaining fairly even throughout the 4-hour period. The phenolsulfonphthalein excretion in 15-minutes is below 20 percent. This group shows evidence of advanced vascular sclerosis throughout the body.

Pattern 6. In this pattern there is a high concentration, early reconcentration, and early water elimination. Both the specific gravity curve and the volume curve are highly unstable and a functional element affecting the renal vascular tree or excretory action is likely. Other renal function tests show no impairment of renal function. Such a curve may be stabilized by barbiturates or aminopyrin.

Other curves indicating a concentrating ability below 1.015 were not studied in detail because these obviously indicate advanced renal functional damage. However, to indicate the pattern of such a tolerance, one patient showed a 10-percent excretion of phenolsulfonphthalein in 15 minutes, a fixed diastolic hypertension, and no visualization of the renal pelvis on intravenous diodrast for a period of 30 minutes. There was marked dilution, overexcretion, and complete failure to reconcentrate. This patient showed no response to splanchnicectomy, although an extended resection of the chain (D5 to L3) was done bilaterally.

The following table shows the correlation of these patterns with the result obtained after sympathectomy. By failure is meant a rise of blood pressure within a year to the preoperative level. A good result is a diastolic blood pressure stabilized between 100 and 110 mm. Hg when it was previously between 130 and 150 millimeters of mercury. An excellent result is a blood pressure below 140/90, at least one year after operation. A re-evaluation of the whole series after 5 years would no doubt give a smaller percentage of good results, and it is simply wished to illustrate a trend.

PATTERN	NUMBER OF CASES	RESULT		
		EXCELLENT	GOOD	FAILURE
1	15	13	2	—
2	42	3	39	—
3	29	—	21	8
4	9	—	1	8
5	*	*	*	*
6	5	—	5	—
Total	100	16	68	16

In the first two groups there were no failures; these belong to the authors' intermittent or continuous but reversible stages of hypertension. The third pattern shows a great number of good results, but failures begin to occur. The fourth pattern, representing failure to reconcentrate and a late water excretion has given very poor results. The fifth pattern, because patients in this group exhibited advanced generalized arteriosclerosis, was not considered to be a surgical group. The significance of the sixth pattern is unclear and will be discussed.

No one test directed against a single organ can be of decisive influence regarding operability. Patients subjected to preoperative study were examined regarding the functional status of their eye grounds, heart, peripheral circulation, and the flexibility of the vascular tree. Neither previous cerebrovascular nor coronary accidents were regarded as prohibitive indications, but advanced cerebral, cardiac, or peripheral vascular damage was regarded as prohibiting surgery. Added to this, failure to concentrate urine below 1.015 after 14 hours

of water deprivation, a 15-minute phenolsulfonphthalein excretion below 10 percent of the dye, or a urea clearance of less than 20 cc. per 100 cc. of blood have been regarded as an argument against operation in the past.

In this series, however, the authors have found 16 failures which do not fall into any of these categories. These operations were technically satisfactory and the general vascular damage was not advanced. Essentially they showed failure to reconcentrate urine in 4 hours, together with a late water excretion; the later the excretion, the more ominous the outlook. It should be emphasized that even Pattern 4 with one good result and 8 failures shows no phenolsulfonphthalein excretion below 20 percent in 15 minutes and the urea clearance does not show consistent diminution below 50 percent of normal. Ever since 1934 the authors' group has accepted patients for splanchnicectomy with very restricted indications, and they now believe that the water tolerance test has given one more indication of irreversible renal damage, which neither renal nor adrenal denervation can alter. This group of 16 patients showed a fair concentration-dilution test and would ordinarily have been regarded as having sufficient renal reserve.

One cannot escape the conclusion that renal damage in hypertensive patients is more likely to be irreversible than cerebral or cardiac damage in spite of the fact that terminally renal failure is the least common cause of death. The vascular obliteration of the kidney may serve as a protective mechanism against progressive injury, but is at the same time uninfluenced by efforts of revascularization.

Patterns 5 and 6 are of special interest. Pattern 5 seems to represent the water elimination of a nephrosclerotic kidney with fixed renal function. On the other hand, Pattern 6 is certainly suggestive of emotional, neurovascular, or neurohormonal influences. Whether such a curve can be stabilized by sympathetic depressants or by central sedation is now under investigation. (Am. Heart J., Aug. '49, G. de Takats and E. F. Fowler)

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Biochemical Studies on Chloramphenicol (Chloromycetin): The structure of the new antibiotic chloramphenicol (Chloromycetin) has been established by the work of Rebstock, Crooks, Controulis and Bartz in the Parke Davis and Co. laboratories as D(-)threo-2-dichloracetamido-1-p-nitrophenyl-1,3-propanediol. The development of a new colorimetric method for aromatic nitro compounds in biological materials has opened the way for studies on the metabolic fate of chloramphenicol, extending the data obtained by others using microbiological assay procedures.

Crystalline chloramphenicol isolated from fermentation sources and synthetic chloramphenicol were used interchangeably in these studies, being identical in chemical structure and properties.

From the results presented here it is evident that chloramphenicol is rapidly absorbed, inactivated and excreted. In man, about 90 percent of the drug administered orally is recovered in the urine in 24 hours, principally in the form of inactive metabolic products which retain the aryl-nitro group intact. Less than 10 percent of the dose is excreted as unchanged chloramphenicol, confirming earlier observations. Evidence is present of the formation of inactive nitro compounds and aryl amines from chloramphenicol by enzymatic processes. Renal plasma clearance figures indicate that chloramphenicol is largely excreted by glomerular filtration, although the inactive metabolic products appear to be excfeted mainly by tubular secretion. The drug is partly excreted in the bile of lower animals, and a large proportion of the total dose is recovered in the intestinal tract.

In the rat, the distribution of chloramphenicol in the tissues is not uniform, with high concentrations being found in the liver and kidneys and low concentrations in the brain and spinal fluid. The principal metabolic products of chloramphenicol have been isolated and identified and will be described elsewhere. (J. Pharmacol. & Exper. Therap., Aug. '49, Part I, A. J. Glazko et al.)

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Nurses of Naval Reserve Needed for Duty on Vessels of Military Sea Transportation Service: Navy nurses will replace Army nurses on vessels of the Military Sea Transportation Service, which will be formally established on 1 October 1949. Approximately 50 sea duty billets on transports are available to inactive members of the Nurse Corps, U. S. Naval Reserve, in the grade of lieutenant and lieutenant (junior grade). Applications are desired now from inactive nurses of the Naval Reserve residing within the continental United States to volunteer for this particular duty for a minimum period of one year. Commencing in December 1949, Navy nurses will be assigned to transports operating out of New York, New Orleans, San Francisco and Seattle to European and Asiatic ports.

Nurses will be ordered to the port of embarkation nearest their home naval district. In submitting application, nurses may request active duty at a naval hospital in her home naval district prior to assignment to the sea billet. Applications should be submitted to the Bureau of Naval Personnel via the commandant of the naval district in which the nurse resides and the Chief of the Bureau of Medicine and Surgery.

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BUMED CIRCULAR LETTER 49-115 20 September 1949

To: Commandants, All Naval Districts (less 10, 15, and 17)
Commandant, Potomac River Naval Command
NMSD, Brooklyn, and NMSD, Oakland

Subj: Medical Allowances for Naval Reserve Training Activities (less aviation)

Refs: (a) BuMed ltr BUMED-4223-CRM:kw over QR/L7-1(2), Serial 10447, dated 16 September 1947.
(b) BuMed ltr BUMED-4223-CRM:adr over QR/L7-1(2), Serial 14316, dated 5 February 1948.
(c) BuMed CircLtr 47-82, dated 26 June 1947.
(d) BuMed CircLtr 47-83, dated 26 June 1947.
(e) BuMed CircLtr 47-99, dated 4 August 1947.
(f) BuMed CircLtr 48-43, dated 13 April 1948.
(g) BuMed CircLtr 48-95, dated 8 September 1948.
(h) BuMed CircLtr 47-100, dated 4 August 1947.
(i) BuMed CircLtr 49-86, dated 12 July 1949.

Encl: 1. (HW) Consolidated Medical Commissioning Allowance Lists for Naval Reserve Training Centers; Electronic Warfare Stations and Drill Quarters; and Vessels or Craft assigned to Naval Districts and River Commands for use in making Naval Reserve Training Cruises of a local and limited nature.

This letter cancels references (a) through (g) and contains information and instructions concerning allowances for medical and dental material for Naval Reserve Training Activities (less aviation).

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BUMED CIRCULAR LETTER 49-116 23 September 1949

To: All Ships and Stations

Subj: Syphilis and Gonorrhea; Recommended Treatment

Refs: (a) BuMed CircLtr 44-217; AS&SL July-Dec 1944, 44-1264, p. 230.
(b) BuMed CircLtr 45-127; AS&SL Jan-June 1945, 45-559, p. 384.
(c) BuMed CircLtr 46-91; AS&SL Jan-June 1946, 46-1256, p. 462.
(d) BuMed CircLtr 47-102; AS&SL July-Dec 1947, 47-735, p. 237.

1. Refs (a), (b), (c), and (d) are hereby cancelled.

2. The treatment of syphilis with penicillin produces such dramatic clinical response and arrest of serologic reactions that evidence of the existence of syphilis may be completely obliterated. It is considered essential that all patients be studied thoroughly in order to confirm or rule out the diagnosis of syphilis prior to the initiation of penicillin therapy. It is recommended that all positive darkfield examinations be confirmed by two medical examiners, and repeat examination be done on all questionable cases. All diagnoses of latent or late syphilis should be considered with particular attention directed to complete history, physical examination, repeatedly positive blood serologic examinations, spinal fluid examinations and the biologic false positive reaction. In all cases where evidence indicating the possibility of latent, visceral or neurosyphilis, or a biologic false positive reaction exists, it is recommended that treatment be withheld pending consultation with a syphilologist and admission to a naval hospital.

3. The Committee on Medicine of the National Research Council has recommended that crystalline procaine penicillin G in aqueous suspension, or in oil plus 2 percent aluminum monostearate be used in the treatment of early (primary or secondary), latent, and late syphilis (excepting neurosyphilis). The recommended schedule calls for intramuscular injection of 600,000 units daily for a total dose of 6 million units administered within a period of 10-15 days. Absolute continuity of injections at daily intervals is not essential, (e.g., treatment may be omitted on Sundays provided the total duration of treatment does not exceed 15 days). For neurosyphilis, it is recommended that crystalline penicillin G (not procaine penicillin) in aqueous solution be utilized every 2 to 4 hours, day and night around the clock, under hospitalized conditions for a total dose of not less than 10 million units administered over a period of from 10 to 20 days.

4. Further schedules for the treatment of relapse or treatment failures are recommended:

(1) First Relapse: Penicillin therapy in established dosage is to be repeated.

(2) Second Relapse: Penicillin therapy in the established dosage with adjuvant mapharsen-bismuth therapy is recommended. Mapharsen-bismuth therapy to be given concurrently with penicillin therapy according to the following schedule:
Mapharsen twice weekly, bismuth subsalicylate in oil once weekly in appropriate dosages for 10 weeks.

(3) For patients who fail after penicillin and adjuvant mapharsen-bismuth therapy, the following treatment schedule of 26 weeks' duration is recommended:

(a) Five weeks mapharsen-bismuth therapy (mapharsen twice weekly, bismuth subsalicylate weekly).

(b) Five weeks mapharsen therapy - two treatments per week.

(c) Six weeks bismuth subsalicylate therapy - one treatment per week.
(d) Five weeks mapharsen - two treatments per week.
(e) Five weeks mapharsen-bismuth subsalicylate according to schedule (3)(a) above.

In cases of neurosyphilis failing to respond to treatment, retreatment with penicillin is recommended. Combined penicillin and malaria therapy may be utilized for the second treatment if the patient is obviously deteriorating.

5. Insofar as practicable, it is recommended that clinical and standard blood serologic follow-up examinations be conducted at monthly intervals within the first year and that a complete evaluation of all patients at the end of one year post-treatment be accomplished. Spinal fluid examination is indicated 6 months post-treatment in primary and secondary syphilis. This examination must include a cell count, quantitative protein determination, complement fixation test, and a colloidal test. In patients manifesting clinical lesions, several weeks of post-treatment observation are required to determine healing or symptomatic arrest.

6. Neurosyphilis is to be followed for a minimum of 6 months prior to final evaluation of the patient's status, if retention in the service appears to be a possible outcome. In neurosyphilis decreasing cell count and protein content of spinal fluid are early and primary indications of favorable response to therapy. Follow-up shall include repeated spinal fluid examinations, cell count, quantitative protein determination, complement fixation, colloidal tests, neurological, ophthalmological, and psychiatric examinations to include adequate psychometric evaluation.

7. It is recommended that the clinical diagnosis of gonococcus urethritis be confirmed by cultural methods wherever possible and especially in doubtful cases. The recommended treatment schedule for uncomplicated gonorrhea is a single dose of 300,000 units of crystalline procaine penicillin G in aqueous suspension, or in oil plus 2 percent aluminum monostearate, administered to the patient in ambulatory status. Patients in whom a favorable response is not present by the third post-treatment day as determined by change in the character or disappearance of the discharge and absence of Neisseria gonorrhoeae by smear or culture are to be retreated utilizing crystalline procaine penicillin G, to a total dosage of 900,000 units over a period of 3-5 days.

8. Those patients with gonorrhea who also have lesions suggestive of syphilis shall be treated conservatively with sulfadiazine and appropriate laboratory examinations shall be conducted to verify or rule out the diagnosis of syphilis.

9. Hospital corpsmen who are fully qualified for independent duty and serving on board destroyers, submarines, small craft or at outlying stations, in the absence of an assigned medical officer, may at the discretion of the commanding officer, treat patients with uncomplicated urethritis, acute, due to gonococcus according to the instructions contained herein. It is considered necessary that all patients so treated be examined by a medical officer at the earliest opportunity following treatment.

10. All Medical Department personnel should be on the alert for evidence of reaction or toxicity to penicillin. A febrile reaction occurring within the first 24 hours may be accepted as a possible Herxheimer reaction, indicating a possible coexistent syphilis. All cases having such a reaction should be reported to a medical officer for continued observation, to rule out coexistent syphilis.

11. Due to the fact that the therapeutic doses of penicillin may mask or retard symptoms of syphilis, it is recommended that individuals treated with penicillin be observed by physical and serological test for syphilis once each month for a period of six (6) months. --BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-117 26 September 1949

To: All Ships and Stations

Subj: Object and Subobject Classification of Medical Department Appropriational Estimates, Obligations and Expenditures

Ref: (a) BuMed Circular Letter 49-102 Navy Department Bulletin 49-612 dated 31 August 1949.

1. In paragraph 1 of ref (a), change first sentence to read, "Effective 1 July 1949".

2. The instructions contained in ref (a) are to become effective at beginning of Fiscal Year 1950. --BuMed. C. J. Brown

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BUMED CIRCULAR LETTER 49-118 26 September 1949

To: All Ships and Stations

Subj: Qualifications for Advancement in Rating of Enlisted Hospital Corps Personnel

Ref: (a) Manual of Qualifications for Advancement in Rating, NavPers 18068.
(b) Art. C-7206(6), BuPers Manual.

1. In clarification of the instructions contained in reference (b), it is the desire of the Bureau of Medicine and Surgery that medical officers or examining boards assigned to determine the professional qualifications of enlisted personnel of the Hospital Corps for advancement in rating, should not recommend those who in their opinion are deficient to the extent of attaining a mark of less than 2.5 (on the basis of 4.0 perfect) in any one of the subtopics listed in the applicable sections of reference (a).

--BuMed. C. J. Brown

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BUMED CIRCULAR LETTER 49-119 27 September 1949

To: All Ships and Stations

Subj: Hospital Corps Technical Courses in Medical Clerical and Medical Property and Accounting Procedures

Refs: (a) Catalog of Hospital Corps Schools and Courses, Revised 1944 (NavMed 367).
(b) Addendum to reference (a).

Encls: (A) (HW) Curriculum and Prerequisites for Instruction in Medical Clerical Procedures.
(B) (HW) Curriculum and Prerequisites for Instruction in Medical Property and Accounting Procedures.

1. Formal courses of instruction in Medical Clerical and Medical Property and Accounting Procedures for enlisted members of the Hospital Corps are hereby established at the Hospital Corps School, Portsmouth, Virginia. It is anticipated approximately 50 students will be assigned to each class.

2. The length of the courses will be six months, consisting of 24 weeks of 40 hours each, currently accelerated to five months consisting of 20 weeks of 40 hours each.

3. Enclosures (A) and (B) outlining the curricula and prerequisites for assignment to the respective courses of instruction are hereby made a part of references (a) and (b) in substitution for those curricula and prerequisites currently contained therein, and will be incorporated in the next revision of the Catalog of Hospital Corps Schools and Courses.

4. The number, ratings and service requirements of students assigned will be incorporated in BuPers quota orders. Classes of instruction will commence on or about 15 November 1949. Hospital corpsmen satisfactorily completing the prescribed courses of instruction will be issued a Certificate of Graduation and will be officially designated as technicians in their respective specialty.

5. This procedure is in accordance with the Navy Personnel Accounting System and the "Manual of Enlisted Navy Job Classifications."

--BuMed. C. A. Swanson

Note: A copy of this letter with the enclosures appears in the 30 September 1949 Navy Department Bulletin.

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BUMED CIRCULAR LETTER 49-120 28 September 1949

To: All Holders of the Manual of the Medical Department

Subj: Advance Change 3-15, MMD

Encl: 1. (HW) Subject Change

1. The enclosed Advance Change 3-15 is effective immediately. It shall be recorded on the "Record of Changes" page in the Manual. The individual paragraph changes are to be inserted in their proper places in the Manual text.

--BuMed. H. L. Pugh

Note: This letter will be distributed as soon as the enclosures are received from the printer.

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BUMED CIRCULAR LETTER 49-121 28 September 1949

To: Holders of the Bulletin of Bureau of Medicine and Surgery Circular Letters

Subj: BuMed Circular Letters; Cancellation of 48-78 and 48-131

This letter cancels BuMed Circular Letters 48-78 and 48-131 and gives the reasons therefor.

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BUMED CIRCULAR LETTER 49-122 29 September 1949

To: All Stations

Subj: Insecticide Aerosol for Use on Naval Aircraft

Ref: (a) BuMed CircLtr No. 49-87 dtd 13 Jul 1949

This letter modifies paragraph 4 of reference (a) by deleting NSD, Mechanicsburg, Pa., NSD, Bayonne, N. J., and NSD, Seattle, Wash., and adds NSC, Norfolk, Va.

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BUMED CIRCULAR LETTER 49-123 Joint Letter 29 September 1949

To: Medical Officers in Command, U. S. Naval Hospitals

Subj: Report of Persons Confined

Refs: (a) Joint BuMed-BuPers ltr of 3 Apr 1947; BuMed-2112-HJR P13-9 BuMed C/L No. 47-42; Pers-520-DC; addressed to NavHosps.
(b) Joint BuPers-MarCorps ltr of 29 Aug 1949, Pers-522-AJA P13-10, to Acts of Shore Establishment within the Cont. U. S.

1. Reference (a) is hereby canceled in view of reference (b) which requires that a Monthly Report of Naval Personnel Confined (Reports Pers 5-12) shall be submitted to the Chief of Naval Personnel by the commanding officer of every Navy and Marine Corps activity, including hospitals, within the continental limits of the Units States (except disciplinary barracks and retraining commands) where established facilities are in operation for the confinement of naval personnel.

--BuMed. C. A. Swanson --BuPers. J. W. Roper

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Op24B/np, NH47/A4-2, Serial 347P24 13 September 1949

To: All Ships and Stations

Subj: Disestablishment of U. S. Naval Hospital, Corona, Calif.

1. The following activity is disestablished effective 1 November 1949:

U. S. Naval Hospital
Corona, California 3435-244

2. Holders of Basic Naval Establishment Plan, Fiscal Year 1949, delete paragraphs 5205 and 5205a.

3. Bureaus and offices concerned take necessary action.

--SecNav. Francis P. Matthews

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NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
WASHINGTON 25, D. C.

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